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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,216	12/04/2001	Keith D. Allen	R-881	6807

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,216	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,10-13,15 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9,14 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0702, 0203*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending.

Election/Restrictions

Applicant's election without traverse of Group III, claims 6-7, 9, 14, and 16-19 in the response filed on 1/30/04 is acknowledged.

Claims 1-5, 8, 10-13, 15 and 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in response filed on 1/30/04.

Sequence Compliance

The instant application is in sequence compliance.

Drawings

New corrected drawings are required in this application because figure 5 is illegible. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance. Providing a substitute Figure 5 is sufficient.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6-7, 9, 14 and 16-19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to a transgenic non-human animal, particularly a mouse, comprising a disruption in a Trp6 gene, wherein the mouse exhibits an increased pain threshold characterized by increased response latency on a hot plate and a method of making the same.

The instant specification has contemplated that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a TRP6 gene. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype related to TRP6. The instant specification has purported that such mice may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1.

The instant specification has disclosed a transgenic mouse whose genome comprises a disruption in SEQ ID NO: 1, wherein the mouse exhibits increased pain threshold. The claims embrace such a mouse and a method of making the mouse. The instant specification has discussed that phenotypes (increased pain threshold) exhibited by such a transgenic mouse could correlate to a disease or disorder. However, the evidence of record does not provide a correlation between increased pain threshold and

any disease or disorder. Moreover, while the specification has purported that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a TRP6, the evidence of record has failed to provide a correlation between any TRP6 related disease/disorder and increased pain threshold. The specification has provided general assertions that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice.

As such, the asserted utility, for the transgenic mouse embraced by the claims, of screening agents that may affect a phenotype of said mouse as provided by the instant specification and encompassed by the claims, does not appear to be specific and substantial. The asserted utility does not appear specific and substantial to the skilled artisan since the evidence of record has not provided any suggestion of a correlation between any TRP6, increased pain threshold, and any disease or disorder. Since the evidence of record has not provided a correlation between increased pain threshold and any disease or disorder, the utility of identifying agents that affect increased susceptibility to seizures and increased sensitivity to pain is not apparent. The evidence of record has not provided any other utilities for the transgenic mouse embraced by the claims that are specific, substantial, and credible.

The asserted utility of the transgenic mouse embraced by the claims is based on the expectation that disrupting the nucleotide sequence set forth in SEQ ID NO: 1 would result in a detectable phenotype in the mouse. The phenotype observed in the transgenic mice embraced by the claims is increased pain threshold. While the phenotypes exhibited by the claimed transgenic mouse are contemplated to be

associated with a disease, the association of increased pain threshold with any disease has yet to be elucidated. In fact the art suggests that results obtained from behavioral studies are greatly influenced by the genetic background of the tested mouse. Crabbe et al (Science, 1999, Vol. 284, pages 1670-1672) observed that laboratory environment and site, test conditions, and genetic strain of a mouse could influence the results of behavioral studies. See pages 1670-1671. For example, Crabbe reports in open field testing, A/J mice were relatively inactive, while C57BL/6 mice were very active. Crabbe further reports that on average mice tested in Edmonton were more active than those tested in Albany or Portland. See page 1671, column 1, the first full paragraph. Crabbe discusses that such inconsistencies in test results can be responsible for observed behavioral phenotypes. Given the inconsistencies in behavioral test results, Crabbe concludes by cautioning that specific behavioral effects observed in mutant (knockout) mice should be not be uncritically attributed to genetic manipulations prior to repeating testing in different laboratories using different strains of mice, if possible. See page 1672, column 1, paragraphs 2-3. With regard to a phenotype of increased pain threshold, Mogil et al (Pain, 1999, 80: 67-82) observe that inbred mouse strains, having different genetic backgrounds, respond differently to pain. See the abstract and throughout the entire document.

Therefore, the references suggest a need to provide independent evidence of an increased pain threshold with a disease or disorder. However, neither the specification nor any art of record provides evidence of the existence of a correlation between increased pain threshold and a disease or disorder, leaving the skilled artisan to

speculate and investigate the uses of the transgenic mouse embraced by the claims. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse embraced by the claims. In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse embraced by the claims to be specific and substantial.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7, 9, 14 and 16-19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 6-7, 9, 14 and 16-19 as they read on transgenic knockout non-human animals, use of embryonic stem cells to make a transgenic mouse, and germline transmission of ES cells:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been

genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a TRP6 gene other than a transgenic knockout mouse whose genome comprises a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al (Journal of Clinical Investigation, 1996) state, "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). Moreover, with regard to claim 9 neither the state of the art nor the prior art of record has provided guidance for use of cells, other than ES cells for production of a transgenic knockout mouse. It would be unpredictable if other cells could be used for the production of a transgenic knockout mouse because other cells may be not totipotent or transmit

through the germline as mouse ES cells do. Even more, claims 6-7, 9, 14, and 16-19 as written do not appear to require germline transmission of the disrupted nucleotide sequence. These claims may be broadly interpreted to read on a single cell comprising a disrupted nucleotide sequence. Since the claims do not require germline transmission of the disrupted nucleotide sequence it would be unpredictable if an ES cell comprises the disrupted nucleotide sequence. As stated above the evidence of record does not support germline transmission of non-ES cells. Also, it would be unpredictable if a disruption of a nucleotide sequence in a single cell would result in a phenotype; the instant specification has not provided any uses for a transgenic mouse that does not exhibit a phenotype resulting from disruption of a nucleotide sequence (see below). As the claims are directed to transgenic non-human animals (claims 6) or a method that requires the use of a cell in the production of a transgenic mouse (claim 9), wherein the cell is interpreted to read on an embryonic stem cell (as in claim 9) comprising a disruption in a TRP6 gene, which must be generated by the introduction of a transgene into an ES cell or transgenic non-human animals, particularly a mouse, that do not exhibit germline transmission of a disrupted nucleotide sequence, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice whose genomes comprise a homozygous disruption of a TRP6 gene as set forth in SEQ ID NO: 1. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse or to make a transgenic knockout mouse with a cell other than an embryonic stem cell.

Claims 6-7 and 14 encompass transgenic non-human animals that comprise a disruption in a TRP6 gene, particularly the nucleotide sequence set forth in SEQ ID NO: 1, that do not exhibit any particular phenotype. Claims 16-19 embrace transgenic non-human animals exhibiting a particular phenotype, wherein a broad interpretation of the claimed animals could read on disruption of a TRP6 gene in a single cell. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Also see Leonard et al (Immunological Reviews, 1995, pages 97-114) who discuss that inactivation of the gene encoding cytokine receptor γ chain in transgenic mice results in a phenotype different from that expected. The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a TRP6. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. Moreover, as the claims read on disruption of a TRP6 gene in a single cell, it would be unpredictable if such a disruption would result in any phenotype. The specification discloses a phenotype exhibited by knockout mice whose genome comprises a heterozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1 is increased pain threshold. See pages 52-54 of the specification. Claims 6-7 as written, do not include a phenotype that differs from the wild-type mouse. One of skill in the art would not know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice that have a phenotype may be used for drug testing according to

the instant specification. The specification overcomes the unpredictability in obtaining a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1, which is asserted to encode a TRP6; however, the claims are not commensurate in scope with the enabled phenotype disclosed in the specification. Inclusion of a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1 or the TRP6 gene in a mouse in the claims would overcome this aspect of the rejection. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER